Fluorinated Lanthanide (III) Probes for 19F magnetic Resonance Imaging.

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BACKGROUND New cancer treatments are being developed that exploit the molecular pathology of the disease; however, for the optimal use of these new treatments, functional imaging probes are required to: image the molecular pathology of the cancer non-invasively in order to select the most effective treatment, demonstrate that the drug is reaching the tumour and interacting with its intended target and provide early evidence of efficacy. (1) Fluorinated probes are of much current interest in ^{19}F magnetic resonance imaging and spectroscopy. The high NMR sensitivity and large chemical shift range (>300ppm), accompanied by a near zero endogenous background, render ^{19}F-MRS and MRI intrinsically attractive for biological studies. (2) A critical limiting feature of this ^{19}F work relates to the slow longitudinal relaxation rate of the ^{19}F nucleus, especially in the CF_3 groups where R1 values are typically 0.5-1 s^{-1}, which determines the optimum repetition time. A solution to this problem is to place the ^{19}F nucleus close to a paramagnetic lanthanide ion, in a stable complex or conjugate, leading to much shorter T1 and T2 relaxation times. (3) In this study we have also used gadolinium complexes as they promote rapid relaxation in surrounding bulk water. Gadolinium is atypical of the lanthanide ions in that it has a spherical electron distribution which gives no dipolar shift but a very fast relaxation in the ligand (which broadens out the ^{19}F signal, in this case). The other paramagnetic lanthanides have a slower relaxation allowing direct observation of signal from the ligand and their non spherical electron distribution gives a dipolar shift contribution.

AIMS The aim of this study was to evaluate recently developed novel fluorinated lanthanide MR probes to measure the effects of tumour vasculature targeting agents on tumour blood flow and kinetics and to compare these with the structurally similar gadolinium based commercial contrast agent gadoteridol (ProHance, Bracco Imaging).

METHODS ^{19}F *in vitro* measurements were carried out on several fluorinated macrocyclic lanthanide (III) complexes (L3Ho, L3Tm, L3Er and L4Ho). L3 is a mono-amide and L4 is a positively charged di-amide complexes with the Ln(III) ions. These were placed in 5mm NMR tubes, cut to fit in the bore of the magnet, using a custom designed two-turn, 12mm, transmit and receive, ^{19}F surface coil. This was then centered in a Varian 7T horizontal bore MR system. ^{19}F relaxation rates were measured using inversion recovery and variable TE spin echo spectroscopy. CSI imaging was also carried out and compared to conventional MR imaging of these complexes. *In vivo* measurements using either L4Gd (2x CF_3 groups) or gadoteridol were carried out on cdi nu/nu mice implanted on the right flank with SW620 human colon carcinoma cells. Measurements were taken 14-21 days after inoculation when the tumours were ~10mm in diameter. Mice had their tail vein cannulated and were restrained in a 39mm ^{1}H quadrature volume coil (Rapid Biomedical) anaesthetized with isofluorane/oxygen inhalation and kept warm using a warm air feedback system. Respiration rate was monitored. Scout images were acquired and slices selected for our ROI, including tumour, kidneys, liver and bladder. A dynamic gradient echo multi-slice sequence was used for imaging. Images were collected 30secs pre and 10mins post contrast agent injection (^{1}H signal acquired to investigate distribution of complex). Parameters included TR = 24 ms and TE = 5 ms.

RESULTS *In vitro* T1 relaxation times for the complexes were as follows: L3Ho 10ms, L3Tm 13.8ms and L3Er 6ms and L4Ho 15ms. This approximately 100-fold reduction in T1 corresponds to an improvement in signal:noise per unit time of about 10-fold. Comparing the conventional imaging to CSI imaging it is clear to see that there is a marked improvement in signal to noise here also (Figure 1). An increase in intensity is seen in the bladder following L4Gd injection but not in tumour or other tissues imaged. Following gadoteridol administration, tumour, kidneys and bladder all showed an increased uptake (Figure 2).

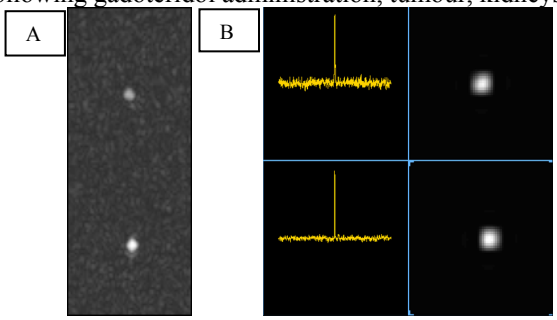

Fig. 1. Conventional MR imaging compared with chemical shift imaging of ^{19}F complexes. A. Gradient echo images B. CSI images.

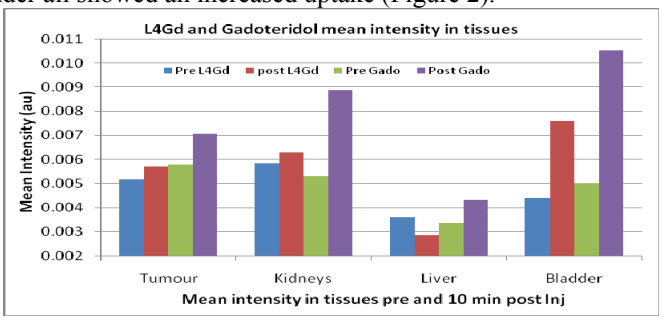

Fig. 2. Increase in intensity in tissues following L4Gd or gadoteridol injection. .

CONCLUSIONS The introduction of CF_3 reporter groups close to the paramagnetic centre in macrocyclic lanthanide (III) complexes allows faster acquisition of ^{19}F magnetic resonance images. We have demonstrated that we are able to image these novel contrast agents *in vivo* and compared their kinetics with conventional ^{1}H contrast agents. Further studies will be made on different complexes and tumour types to assess the potential for using other ^{19}F-lanthanide probes for non-invasive assessment of tumour microenvironment and drug efficacy.

REFERENCES 1. Brix-G et al. *Magnetic Resonance Imaging, 23, 2005, 967-976.* **2.** Kenwright-AM et al. *Chem. Commun., 2008, 2514-2516.* **3.** Senanayake-PK et al. *Chem. Commun., 2007, 2923-2925.*